The Fish Foundation
Omega 3 for Hearts and Minds

P.O. Box 24,
Tiverton, Devon EX16 4QQ
Tel: 01884-257547 Fax: 01884-242757

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630, Fishers Lane, Rm. 1061
Rockville, MD 20852.
USA

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Re: Food Labelling; Health Claims and Label Statements
Docket No. 91N-0103
Request for Scientific Data and Information
"Consumption of omega-3 fatty acids may reduce the risk of coronary heart disease"

Fish Foundation submission to FDA in support of health claims for fish and fish oil.

Introduction

It is the belief of the Fish Foundation that it is important for future public health to permit limited claims with regard to the role of the long chain omega-3 polyunsaturates in helping to reduce the risk of death from heart attack.

The evidence in support of this contention comes from studies of the epidemiology of fish eating populations, from laboratory and clinical studies of the various mechanisms involved, and most importantly from intervention studies which have shown a lower rate of death in subjects with an enhanced intake of the long chain omega-3 polyunsaturates compared to controls. Each of these three areas of evidence will be outlined in what follows.

The Evidence

1. Epidemiological Evidence

One of the first such observations was reported by Kronman & Green(1980), who found that Eskimos living in their traditional areas had virtually no heart disease. Dyerberg & Bang(1978) investigated this, and concluded that the "cause" of this "effect" was most likely the relatively large intake of omega-3 polyunsaturates which is a feature of the traditional Eskimo diet. Since then, several other studies (Dolecek & Grandits, 1991, Kromhout Bosschieter & Coulander, 1985) have revealed much the same thing, i.e. that populations with a high intake of fish (or more correctly, the omega-3 polyunsaturates from fish) have a low incidence of death from heart attack. In 1997 Daviglus et al reported a 40% reduction in risk of death from a heart attack in men eating an average of as little as 35g of fish daily. In 1998 these ideas have been confirmed by large American studies (Albert et al, 1998), with up to a 50% reduction in the risk of death from a heart attack among weekly fish eaters when compared to those who ate fish only infrequently.
Evidence on stroke is not quite so plentiful, but Keli et al published a study in 1994 providing evidence that weekly fish consumption was associated with a 50% lower risk of death from stroke.

2. Supplementation Studies

This type of study examines what happens when people are given additional omega-3 polyunsaturates, either in the form of fish itself, or in the form of oil extracted from fish. The latter type of study is more meaningful scientifically, since the addition of the oil is the only change made. When fish is used, other components of the fish, such as vitamins, selenium, iodine or other minerals, might influence any changes which are observed, making the interpretation of the results less certain.To date, the supplementation studies have demonstrated that adding the long chain omega-3's to the diet results in:-

-lower serum triglyceride levels,
-lower blood pressure,
-lower risk of blood clotting,
-lower blood viscosity, and
-lower risk of the development of irregular heartbeat (arrhythmia).

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All these factors contribute to the reduction in risk of death from a heart attack, and all except the last contribute to reduced risk of stroke also.

a) Triglyceride lowering studies.

Among the first intervention studies carried out in this field were those of Saynor and his colleagues in Sheffield. They were the first to observe the triglyceride lowering effects of the omega-3's, and published this information in 1980 (Saynor & Verel). Later studies by the same authors (Saynor & Gillott, 1992) and many others, 65 of which have been reviewed by Harris (1997), showed the same thing, i.e. that addition of long chain omega-3 polyunsaturates to the diet results in a substantial (30-50%) and sustained (over 7 years) fall in serum fasting triglyceride levels. In general, the triglyceride lowering effect is greater in those with high levels at the start of treatment. The extent to which risk of heart disease is associated with raised serum triglyceride levels has long been contentious. Recently, opinion has begun to favour recognition of triglyceride as an independent risk factor, following a paper published by Hokanson and Morris in 1996. They reviewed more than 17 studies, involving nearly 60,000 subjects, and concluded that elevated serum triglyceride levels confer additional risks, over and above those conferred by other factors.

b) Blood pressure lowering studies

One of the first papers to report a blood pressure lowering effect of fish oil was that by Mortensen and colleagues, published in 1983. They gave a group of healthy volunteers 3g of omega-3 daily for four weeks, and found a 4mm fall in diastolic blood pressure, which was statistically significant. Since that time, a number of other (though not all) studies have shown similar results (Sanders & Hind, 1992, Schmidt et al,1992). In 1993, Morris et al published a meta-analysis of 31 studies, and concluded that fish oil does have a blood pressure lowering effect, the magnitude of which is -0.35 to -0.66 mmHg per gram of omega-3 per day. As with triglyceride lowering, the effect of the omega-3's on blood pressure is greater in subjects with higher blood pressure at the start of treatment.

c) Studies on blood clotting

Such studies are notoriously difficult to interpret, mainly because blood is a multifunctional fluid which normally exists only within an intact blood circulatory system. To measure changed clotting behaviour it must be removed from that system, and in so doing, changes are made which might have a large bearing on the results obtained. With these caveats in mind, there are two types of research which throw light on the question of whether or not increasing dietary intake of the omega-3's reduces the likelihood of a blood clot forming within an intact blood vessel.

The first, and simplest, is to measure the time it takes for a cut to stop bleeding. Using standardised techniques, it is possible to demonstrate differences in the "bleeding time" in this way. Sanders,Vickers and Haines (1981) were the first to report an increase in bleeding time after a fish oil supplement (in this case, cod liver oil). They also found other changes in bleeding parameters which were consistent with a reduced propensity to form blood clots. Schmidt et al (1992) also found an increase in bleeding time following 9 months on a 4.4g/day supplement of omega-3's . Other investigators have subsequently confirmed these findings.

The second way of assessing such changes is to measure various parameters in a sample of blood drawn after a period of time during which the diet has been supplemented either with fish oil or a placebo. Using this technique, Sanders & Hinds (1992) showed that fish oil supplementation brought about a lower platelet aggregation response to collagen, and produced less thromboxane B2, a potent aggregation stimulant. Malle et al (1991) also found reduced aggregation responses to collagen and ADP, and reduced thromboxane B2 production in subjects given 6g or omega-3 daily for 6 weeks. Tremoli et al (1995) found much the same thing. The whole subject of bleeding responses to fish oil supplementation was reviewed by Knapp in 1997, who concludes that the long chain omega-3 polyunsaturates do exert a bleeding prolongation effect, and probably result in increased flexibility of the erythrocyte membrane.

d) Blood viscosity lowering studies

Reducing the viscosity of blood benefits the circulatory system, and reduces workloads on the heart. One of the first studies which reported a reduction in whole blood viscosity in healthy subjects given fish oil was that by Cartwright et al (1985). The same group also published results on a group of peripheral artery disease patients which showed similar findings (Woodcock et al, 1984). Toth et al (1995) showed comparable results on a group of heart disease patients.

e) Arrhythmia studies

Studies on the human heartbeat mechanism are difficult to carry out, because of the risks involved to the subjects. For this reason, most of the information on this subject has come from studies carried out on animals, or on model systems. McLennan et al, in 1993 reported that marmoset monkeys were less susceptible to experimentally induced rhythm disturbances (arrhythmias) when fish oil was included in their diet. Charnock (1994) reported further evidence in the same animal model. Siebert et al (1993) fed various diets to laboratory rats, and found less arrhythmia when fish oil was included. Billman et al (1994) used an anaesthetised dog model to confirm the antiarrhythmia properties of omega-3 polyunsaturates. Leaf and Kang (1996) reviewed the various animal and model system information available, and concluded that there was a very strong likelihood that similar effects would be observed in humans.

Three studies have reported beneficial effects in human subjects. Christensen(a) et al (1995) used 24 hour Holter recorders to investigate rhythm disturbances in a group of 24 patients who were being investigated for heart rhythm problems. There were fewer rhythm abnormalities in the fish oil group compared to the group given corn oil, but the size of the difference was not large enough for the investigators to be sure it was not due to chance alone. Sellmayer et al (1995) found a 44% reduction in abnormal heartbeats in a group or 34 patients given fish oil, compared with only a 15% reduction in a similar group given sunflower oil . Christensen(b) et al (1998) examined heart rhythm disturbances in a group of patients with kidney disease (in whom heart rhythm problems are often found) and reported that the use of a fish oil supplement led to fewer heart rhythm disturbances compared to placebo.

3. Intervention Studies

The epidemiology studies and the supplementation studies provide valuable clues as to what happens when the level of omega-3 in the diet is increased, but they do not provide the ultimate proof that eating more fish, or fish oil, will lead to fewer premature deaths. In the ultimate analysis, we must all die of something, the only thing we can do is to prevent premature death, and this is what fish and fish oil can do.

The proof of this comes ultimately from intervention studies, that is to say studies in which a change (or an intervention) is made in the lifestyle or diet (or both) of a group of people, and the effects compared to those seen in a similar group which did not have the intervention. When it comes to demonstrating that eating more fish can reduce premature heart deaths, there are formidable problems. This is primarily because of the large numbers of people and the long time they must be followed to be able to show conclusively that eating more fish results in less premature cardiac death. Not only is the cost high, but there is a great difficulty in getting subjects to sustain the intervention over long time periods. To get around some of these difficulties, the studies carried out to date have used as subjects people that have already been identified as being at higher than normal risk of a heart attack. Using subjects such as this, smaller numbers can be used, and the time periods needed should be shorter. Hence the projects become feasible.

The first meaningful intervention study to examine the question of whether the omega-3 from fish can have any impact on heart deaths, was the DART study carried out in Cardiff, Wales by the Medical Research Council, and reported in 1989. Burr(a) et al (1989) used as subjects 2000 men who had already survived one heart attack. The men were divided into groups. 1000 of the subjects were advised to eat more oil-rich fish, such as herring, mackerel, sardines, salmon etc. Twice weekly was the goal. For those unable or unwilling to eat the fish, fish oil in capsules (MaxEPA, 3g/day) was provided. The other 1000 men were not given the fish eating advice, but were advised to eat less fat, or more fibre, or both. After two years, there were 30% fewer deaths in the fish group compared to the group not advised to eat more fish. In a separate analysis Burr(b) ,Sweetnam & Fehily (1994) examined the results for those men that ate fish compared to those taking the fish oil capsules instead. In essence, there was no difference, showing that the benefit came from the oil in the fish, rather than any other component (such as selenium, iodine, proteins or vitamins etc.).

A second intervention study was reported in 1997, again using patients who have survived a suspected heart attack. This study, by Singh et al (1997), was smaller, using 120 patients in the fish oil group, and a similar number in the placebo group, and the subjects were followed for one year. The fish oil patients took 6 g of fish oil (MaxEPA) daily, providing 2g of omega-3 long chain polyunsaturates. Total cardiac events were significantly fewer in the fish oil group compared to the placebo group, and the rate of death from heart attacks was about half in the fish oil group compared to that in the placebo group. The fish oil group also showed significantly less rhythm disturbances (arrhythmia), and less angina than the placebo group.

More recently an Italian study (GISSI, 1999) has shown a 20% reduction among nearly 12,000 survivors of a heart attack given 1g capsules of fish oil containing 85% omega-3 polyunsaturates. The trial lasted over 3 years, and is the strongest proof available that consuming more of the omega-3

polyunsaturates will reduce subsequent risk of death from a heart attack. The benefits of fish oil in this study came on top of whatever benefit was derived from the orthodox pharmacological treatment the subjects were receiving, because this was maintained during the trial. This trial was analysed on an "intention to treat" basis, which necessarily results in an understatement of whatever effect fish oil had.

Conclusion

The Fish Foundation contends that the evidence presented above, of significant and sustained benefit, in relation to the long history of safe dietary use of fish and fish oil justifies the permitting of label and advertising claims along the lines of ..."scientific studies confirm that consumption of omega-3 fatty acids may reduce the risk of coronary heart disease".

Such a conclusion was also reached in the UK Government's Department of Health Report on Nutritional Aspects of Cardiovascular Disease, published in 1994. This report recommended that per capita intake of the long chain omega-3 polyunsaturates from fish should increase by 100%.

Ray Rice, M.S., Ph.D., MIFST.
Chief Executive,
The Fish Foundation,
P.O.Box 24,
Tiverton,
Devon EX16 4QQ,
U.K.

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